OUTLINE

- Medical Device Innovation Consortium
- External evidence
- Spring workshop
- Framework
- Future directions
WHAT IS MDIC?

A 501 (c)(3) and public-private partnership created with the sole objective of advancing regulatory science of medical devices for patient benefit.
DEFINING REGULATORY SCIENCE

The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.
"What we've lacked is a structure like the Medical Device Innovation Consortium that allows for a larger number of parties to come together to develop these projects on an ongoing basis - a significantly more effective way to do research."

- Jeffrey Shuren, MD, JD
  Director of CDRH
  MedPage Today, December 4, 2012
OUR CORE INITIATIVES DRIVE OUR SHARED VISION WITH CDRH

MDIC facilitates a number of programs and activities that support CDRH strategic priorities. These programs are housed within four core initiatives of MDIC.

- CLINICAL SCIENCE
- DATA SCIENCE AND TECHNOLOGY
- HEALTH ECONOMICS AND PATIENT ACCESS
- NATIONAL EVALUATION SYSTEM FOR HEALTH TECHNOLOGY COORDINATING CENTER (NESTcc)
HEALTH ECONOMICS AND PATIENT ACCESS

Aims to create predictability and transparency of evidentiary requirements for coverage and improve pathways for coverage, coding and payment to speed patient access and amplify the patient voice in selection of treatment options.

- Promote predictability of evidentiary processes
- Improve pathways for coverage, coding and payment to speed patient access
- Compliment existing efforts of trade associations
CLINICAL SCIENCE

Addresses barriers to collecting adequate clinical evidence in the support of new medical technology by creating blueprints for innovative clinical trials techniques, developing standards and metrics for effective clinical trial designs and encouraging the collection of adequate and appropriate clinical and patient preference data.

- Early Feasibility Studies (EFS)
- Science of Patient Input (SPI)
- Clinical Diagnostics (CDx)
DATA SCIENCE AND TECHNOLOGY

Creating tools and methods to use advanced data analysis techniques and new technology to accelerate the collection of clinical data, remove barriers to patient access and monitor product safety, quality and effectiveness.

- Case for Quality (CfQ)
- Computational Modeling and Simulation (CM&S)
- External Evidence Methods
- Cybersecurity
DATA SCIENCE AND TECHNOLOGY

Creating tools and methods to use advanced data analysis techniques and new technology to accelerate the collection of clinical data, remove barriers to patient access and monitor product safety, quality and effectiveness.

Case for Quality (CfQ)
Computational Modeling and Simulation (CM&S)
External Evidence Methods
Cybersecurity

EEM is an extension/superset of earlier work done on Virtual Patients within the CM&S workstream
EXTERNAL EVIDENCE
EXTERNAL EVIDENCE

- In context of a clinical trial, **external evidence** refers to data *generated* outside the current trial, but *analyzed* together with the current trial data.
- Separation of data generation and data analysis processes is an important concept.
- Can include RWE/RWD from registries, claims, EHR.
  - Not restricted to such data.
- Examples of external evidence include:
  - Historical trial data matched to current study data via propensity scoring.
  - Historical trial data used as an informative prior together with new data.
  - Virtual patient data (generated through modeling and simulation) combined with new real patient observations.
  - OPC or PG values determined from literature to be used a benchmark against new clinical data.

**Leveraging External Data to Generate Evidence: A Case Study**

Heng Li
Vandana Mukhi
Lilly Yue
FDA/CDRH
Example #1

• Investigational device – Left Ventricular Assist Device

• Study design – Prospective comparative study for pre-market approval

• External data source - Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)

• Use of external data – Concurrent control group

• Statistical method - Propensity score stratification

Example #2

• Investigational device – Transcatheter Aortic Heart Valve

• Study design – Comparative study for indication expansion with historical control

• External data source – The surgery arm of a completed randomized clinical trial

• Use of external data – Historical control group

• Statistical method - Propensity score stratification

EXTERNAL EVIDENCE

- **Scope issues**
  - Focus here is on cases with a mixture of external and current data
  - Purely external data is out of scope
  - Meta-analysis of published literature
  - Claims data comparative effectiveness studies
  - Many registry based analyses using RWE/RWD
  - RWE/RWD issues well covered by existing guidances
EXTERNAL EVIDENCE

- Easy cases
  - Merging in mortality information for all subjects from Social Security Death Index for a US study
  - Merging in hospital costs for all subjects
    - Data generated during study, but captured without regular site staff
- Harder cases
  - Using only historical data for the control arm, and only current data for the experimental arm
    - Especially hard if data capture mechanism differ substantively between arms
  - Working with a novel virtual patient model derived from M&S
    - Unclear what level of validation is appropriate
in silico clinical trial

An in silico clinical trial is an individualised computer simulation used in the development or regulatory evaluation of a medicinal product, device, or intervention.

Avicenna Alliance: in silico Clinical Trials Roadmap

Transforming the Medical Device Innovation Ecosystem with in Silico Clinical Trials

Tina Morrison, Ph.D.
Deputy Director, Division of Applied Mechanics
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
U.S. Food and Drug Administration
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Three unique examples of *in silico* clinical trial approaches

1. Digital evidence has dramatically minimized the need for confirmatory clinical studies for MRI safety.

2. Digital evidence supported the same regulatory conclusion with a “in silico only” clinical trial.

3. Digital evidence, with statistical methods, can reduce the size of a real clinical trial.

Keywords:
- NEJM
- FDA viewpoint
- VICTRE
- JAMA
- MDIC & virtual patient

Transforming the Medical Device Innovation Ecosystem with *In Silico* Clinical Trials

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Digital Evidence as External Evidence

Implementing the Virtual Patient Model with Evidence from Computer Simulations

Collaboration between FDA & Dassault Systèmes to develop a digital platform to:

1. Use physics-based models with statistical models to demonstrate how virtual patients from simulation can be combined with real patients from clinical trials

2. Demonstrate a possible “submission of the future” to create a new “review experience”
   o Develop a platform to incorporate digital, clinical and real-world evidence which supports product-lifecycle-management and continuous improvement

Living Heart Applications: Virtual Design & Testing of Cardiovascular Devices

Opportunity for medical devices and pharmaceuticals

- Heart Disease
- Pacemaker Leads
- Stents
- Valves
- LVAD

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SPRING WORKSHOP
EXTERNAL EVIDENCE METHODS
Executives & Fellows Meeting

April 2, 2019
# SPRING WORKSHOP

## Session 1: Moderated by Ted Lystig (Medtronic)

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<td>Hilda Scharen-Guivel (FDA) &amp; Nandini Duraiswamy (FDA)</td>
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<td>Overview of NESTcc Program</td>
<td>Robbert Zusterzeel (MDIC/NEStcc)</td>
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<td>Review: EEM Mock Submission</td>
<td>Tarek Haddad (Medtronic)</td>
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<td>Case Study: Bayesian Power Prior with a discount function for a mortality endpoint</td>
<td>Hong Zhang (Abbott)</td>
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<td>Case Study: An R Package for Design and Analysis of Adaptive Bayesian Clinical Trials</td>
<td>Thevaa Chandereng (Medtronic)</td>
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<td>Clinical Study Design via Adaptive Bayesian Power Prior: Fine-tune the Degree of Borrowing from a Single Prior Dataset at Interim Analysis</td>
<td>Laura Thompson (FDA)</td>
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<tr>
<td>Transforming the Medical Device Innovation Ecosystem with In Silico Clinical Trials</td>
<td>Steve Levine (Dassault Systemes) &amp; Tina Morrison (FDA)</td>
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Propensity Score Based Methodology

**Session 2: Moderated by Vandana Mukhi (FDA)**

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<td>Leveraging External Data to Generate Evidence: A Case Study</td>
<td>Heng Li (FDA)</td>
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<td>Incorporating Real-World Data for Regulatory Decision-Making: Statistical Approaches for Augmenting Patient Cohort in Investigational Studies</td>
<td>Lilly Q. Yue (FDA)</td>
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Afternoon Breakout Sessions

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<td>Chris Mullin (NAMSA)</td>
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<td>Registry Data</td>
<td>Yun-Ling Xu (FDA)</td>
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<td>Modelling &amp; Simulation</td>
<td>Tarek Haddad (Medtronic)</td>
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<tr>
<td>Admin Data (EHR, Claims etc)</td>
<td>Ted Lystig (Medtronic)</td>
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FRAMEWORK

- General framework being developed through MDIC EEM WG
  - MDIC EEM WG: Medical Device Innovation Consortium External Evidence Methods Working Group

- Framework consists of multiple elements
  - Classification of external data sources
  - Categorization of how current and external data will be combined
  - Compatibility steps
  - Cataloguing/development of certain methods
  - Charting of regulatory interactions
CLASSIFICATION OF EXTERNAL DATA SOURCES

- Modeling & Simulation
  - E.g., virtual patients for fracture propagation in pacemaker leads, or for glucose-insulin dynamics in diabetics with insulin pumps

- Registry data
  - Sources that generally require informed consent
  - Many therapy specific examples coordinated via NESTcc

- Administrative data
  - Sources that generally do not require informed consent
  - Frequently deidentified
  - Claims (CMS, BCBS, others), Warranty information, Electronic Health Records, Laboratory Information System (for diagnostics)

- Historical study data
  - Study or trial
  - Could include: US, OUS; study level or IPD; roll-in subjects
FRAMEWORK

- Categorization of how current and external data will be combined
  - Some external data in both experimental and control
    - E.g., Combined analysis of pilot phase and pivotal phase data
  - Some external data in control arm only
    - E.g., adaptive borrowing of historical data for a standard therapy
  - All external data in control arm only
    - E.g., use of an OPC or PG when comparing to an older standard
  - All external data in both experimental and control
    - Out of scope
    - Could be analysis of claims data alone, with no directed intervention
Compatibility steps

- Appropriate steps need to be taken to justify combining data from different sources
- Need to be very cautious when treatments are potentially confounded with database
- Initial assessment of compatibility largely a Clinical judgment
- Propensity score methods very popular, but many variants available
  - 1:1 or 1:k matching; coarsened exact matching; stratification; weighting by inverse probability of treatment (IPTW)
- Some recent work suggest avoiding direct PS matching
FRAMEWORK

- Cataloguing/development of certain methods
  - Much recent development has centered on variations of the Bayesian power prior model (including the previous talk)
  - Validity of model assumptions could vary greatly across therapy examples
  - Catalog will be more useful as a repository of examples than as any guarantee of suitability
FRAMEWORK

- Charting of regulatory interactions
  - For M&S approaches in particular, not currently clear how best to coordinate interactions between sponsors and the agency for gaining endorsement of a new model
  - Not clear that a given model can/should be considered completely independently of a new therapy
  - Even for registry and related data, unclear how to ensure proposals are evaluated by persons with most relevant expertise
  - Akin to issues when developing drug/device combination products
    - Considering which data elements are most relevant, instead of which mechanisms of action are most relevant
FUTURE DIRECTIONS

- Real world data/evidence (RWD/RWE) is increasingly of interest
  - Vital to ability to generalize findings beyond specialized clinics, researchers
- Access to RWD remains a challenge
- Need to think more broadly about issues in incorporating historical data and M&S evidence as well (not just restrict attention to RWD)

- Want to combine RWD (or other external information) with prospectively collected clinical trial data
- Questions for use of external data:
  - What data do you have? (Characterization)
  - How good is it? (Quality)
  - What do you want to do with the data? (Suitability)
  - How will you do it? (Methods)
- Public private partnerships such as MDIC and CTTI will be instrumental in advancing such activities
  - MDIC EEM WG will be a key contributor to these efforts
THANK YOU!

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